IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/697,720
Appellant	:	STANLEY N. COHEN, ET AL.
Filed	:	OCTOBER 29, 2003
Title	:	MAMMALIAN TUMOR SUSCEPTIBILITY GENES AND THEIR USES
Confirmation No.	:	3761
Art Unit	:	1642
Examiner	:	MISOOK YU
Atty Docket No.	:	FUNC-0027-CO5

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P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' APPEAL BRIEF

Sir:

This Brief is presented in support of the Notice of Appeal, filed July 16, 2007, from the final rejection of Claims 29-33 of the above-captioned application, as set forth in the Final Office Action mailed April 19, 2007.

The requisite fee of $255.00 for filing this Brief is concurrently being paid electronically.

A request for extension of time accompanies this response. The requisite fee of $820.00 for a four-month extension of time is concurrently being paid electronically.

An oral hearing is requested. A separate request for oral hearing with the appropriate fee will be filed within two months of the Examiner's Answer.

I. REAL PARTY IN INTEREST

The real party in interest is the Board of Trustees of the Leland Stanford Junior University. Functional Genetics, Inc. of Gaithersburg, Maryland is the exclusive licensee of the application in on appeal.

II. RELATED APPEALS AND INTERFERENCES

There are no other prior or pending appeals, interferences or judicial proceedings that may be related to, directly affect, be directly affected by, or have some bearing on the Board's decision.

III. STATUS OF CLAIMS

Claims 29-30 are rejected, Claims 31-33 have been withdrawn from consideration by the Examiner. The claims pending on appeal are Claims 29-34. A copy of the claims is attached hereto as the Claims Appendix. Applicant notes that in the final Office Action, Examiner addressed only claims 29-33; however, claims 29-34 were presented for examination. Applicant assumes that Examiner's omission of claim 34 was the result of mere oversight and that Examiner would intend to restrict claim 34 on similar grounds to claim 33 from which it depends.

IV. STATUS OF AMENDMENTS

Claims 1-23 were originally filed in the current application on October 29, 2003. Claims 1-23 were canceled, and Claims 24-28 were added by Applicant's Preliminary Amendment, also filed October 29, 2003. In the Office Action mailed August 31, 2006, the Examiner rejected Claims 24-28. Claims 24-28 were cancelled and Claims 29-34 were added in Applicants' Amendment filed February 26, 2007. In the Office Action, dated April 19, 2007, the Examiner's finally rejected Claims 29 and 30. It is assumed that Examiner intended to restrict claim 34 on the same basis as independent claim 33.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention relates to an isolated polypeptide comprising the sequence of amino acid residues 11-390 of SEQ ID NO:4. The invention further relates to an antibody generated against the protein having the sequence 11-390 of SEQ ID NO:4, and the complex formed thereby.

VI. GROUNDS OF REJECTION TO BE REVIEWED

1. The Examiner imposed a restriction requirement among the following inventions:

   I. Claims 31 and 32, drawn to a complex comprising protein and antibody; and

   II. Claim 33 and 34, drawn to antibody.

2. Claims 29 and 30 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the written description requirement.

3. Claims 29 and 30 stand rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by GenBank referencing Accession No. U8213 (dated June 4, 1998) and U.S. Patent No. 5,92,016 **(Brie et al.)**.

4. Claim 30 stands rejected under 35 U.S.C. § 101 because the claimed invention is purportedly directed to non-statutory subject matter.

VII. ARGUMENT

A. Rejection of Claims 29 and 30 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

1. The exact sequence recited, and its functions, are reflected in the application as originally filed in 1996

The Examiner has rejected Claims 29 and 30 as lacking written description in n the specification. This is a two fold rejection. The Examiner asserts that the recitation "amino acids 11 – 390 of SEQ ID NO:4" lacks support in the specification as filed. Respectfully, it is unclear how this can be. All 390 amino acids of Sequence No. 1 are set forth in the specification as filed. There is no question what is described by the word of the claims – it is that portion of the specification of the application as originally filed includes all but the first ten amino acids.

What is not described? Perhaps the Examiner's position is founded on the proposition that the specification as originally filed does not particularly point to the sequence 11 – 390 out of all possible sequences identified by the recitation of Amino Acids of sequence 4. While the Examiner does not so indicate, if in fact that is the basis for this aspect of the written description rejection, it is incorrect. The application, as originally filed, identified this exact sequence of amino acids as SEQ ID No. 4. While it is true that the specification was amended by Preliminary Amendment to set forth the entire full sequence as later determined, the sequence listing as originally filed included as a separate sequence SEQ ID No. 4, which is residue for residue identical to the aspect

of the claims embraced by amino acids 11 – 390 of SEQ I.D. No. 4 in the application as amended. Thus, since at least 1996, and earlier, the application on appeal, and its parents, have included the exact sequence of amino acid residues that is residues 11 – 390 of SEQ ID No. 4. There is no new matter. A rose, by any other name, would smell as sweet. An amino acid sequence of 380 amino acids, each one identified by name in sequence, is the same sequence, whether referred to as SEQ ID No. 4 before the amendment, or residues 11 – 390 after the amendment.

The examiner also seems to assert that because the claims embrace a genus of polypeptides, they are not supported by a written description. The examiner's attention is specifically drawn to the fact that this sequence, which corresponds to Sequence 4 in the parent application as originally filed more than a decade ago, is identified as a TSG101 polypeptide, (as well those embracing it or related to it have specific functionality), see page 4 of the specification, lines 24 -28. The specific functions and utilities of this family or "genus" of polypeptides, as well as the antibodies prepared therefrom is described in detail at pp. 14, l. 23 – p. 23, l. 11. To the extent the Examiner's characterization of the claims as being directed to a structure where "there is not even identification of any particular function associated with the genus of polypeptides comprising the specifically recited portion" is the basis for the second half of the written description rejection, it is a fundamentally factually incorrect characterization.

2. The law does not confine applicants for patent to only the specific composition shown, where the exact composition, and its functions, are set forth

In any event, notwithstanding the lack of clarity regarding the actual basis of the asserted lack of written description, application of such a rejection to the claims on appeal does not reflect the current state of the law. In this regard, one must bear in mind that applicants claims are drawn to a composition of matter whose exact sequence is given in the specification as filed. To satisfy the written description requirement, "the applicant does not have to describe exactly the subject matter claimed." Instead, "the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). The test for sufficiency of written description support has also been phrased as whether the applicant conveys "with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention." *Id.* at 1563-64. However, even though articulation of written description in terms of 'possession' is often appropriate and meaningful for policing priority, *Enzo Biochem Inc. v. Gen-Probe*, 323 F.3d 956, 969 (Fed. Cir. 2002), "[a]pplication of the written description requirement…is not subsumed by the 'possession' inquiry. A showing of 'possession' is ancillary to the statutory mandate that the specification shall contain a written description of the [claimed] invention." *Id.* at 969.

It is true that a more particular written description standard is applied to inventions embracing chemical and biotechnological compositions. With regard to claims directed to sequences of DNA, the court in *Eli Lilly* held that "[a]n adequate written description of a DNA…requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention. Accordingly, an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Reagents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997). As a result, courts have generally required applicants claiming a novel DNA or protein sequence to disclose its exact structure or sequence identity to be entitled to the invention.

However, the court in *Eli Lilly* did not hold that all functional descriptions of genetic material fail to meet the written description requirement. *Enzo Biochem* at 964. In adopting the USPTO Guidelines for Written Description, the court in *Enzo Biochem* noted that "the written description requirement can be met by showing that an invention is complete by disclosure of *sufficiently detailed, relevant identifying characteristics*, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Enzo Biochem* at 964 (emphasis added).

Since *Eli Lilly*, courts have carved out limitations to the strict general rule that genetic inventions must be described by its exact sequence or structure in the specification to satisfy the written description requirement. See *Enzo Biochem v. Gen-Probe*, 323 F.3d 956, (Fed. Cir. 2002) (biological deposit incorporated by reference fulfills written description); *Randolph J. Noelle v. Lederman et al.*, 355 F.3d 1343, (Fed. Cir. 2004) (antibody supported by description of fully characterized antigen); *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, (Fed. Cir 2004) (stated in dicta: "given the sequence of a single strand of DNA or RNA, it may therefore have become a routine matter to envision the precise sequence of a complementary strand."); *In re David Wallach*, 378 F.3d 1330, (Fed Cir 2004) ("the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it..."); *Capon v. Eshhar*, 418 F.3d 1349, (Fed Cir 2005) (*Eli Lilly* does not require re-description of sequences known in the art); *Falkner v. Inglis*, 448 F.3d 1357, (Fed Cir 2006) (*Eli Lilly* does not require examples, actual reduction to practice, or disclosure of known sequences.)

However, in all cases since *Eli Lilly* where the Federal Circuit seriously considered the sufficiency of written description support for a claimed chemical compound or DNA/protein sequence, the patent in question did not contain *ipsis verbis* or *in haec verba* support. In *Eli Lilly*, for example, the applicant did not provide the sequence of the claimed human insulin cDNA and relied on the rat insulin cDNA and the

human insulin protein sequences for support. In *Enzo Biochem*, reliance was on a biological deposit since the specification did not directly provide the claimed sequence. In *Purdue Pharma v. Faulding*, 230 F.3d 1320, (Fed Cir 2000), the issue was written description support for a method of treating a human with an analgesic compound defined according to functional characteristics. In *Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, (Fed. Cir. 2003), the issue was whether a person of ordinary skill in the art would know all of the vertebrate or mammalian cells that could be used to express human erythropoietin from the examples of cells disclosed. In *University of Rochester v. G.D. Searle*, 358 F.3d 916, (Fed Cir 2004), the question focused on a method of treating a human using an inhibitor of the Cox-2 enzyme where the inhibitor had not been identified by name or structure. In *In re David Wallach*, 378 F.3d 1330, (Fed Cir 2004), the issue was whether there was sufficient written description support for DNA molecules encoding for a protein where there was only a partial sequence for the protein. In *Capon v. Eshhar*, 418 F.3d 1349, (Fed Cir 2005), the question was whether a chimeric gene was supported by component sequences that had already been individually disclosed and understood in the prior art. In *Invitrogen v. Clontech*, 429 F.3d 1052, (Fed Cir 2005), the issue was whether a claim directed to "an isolated polypeptide having DNA polymerase and substantially reduced RNase H activity…encoded by a modified reverse transcriptase nucleotide sequence" was supported where the DNA sequences were supplied from the prior art. Finally, in *Falkner v. Inglis*, 448 F.3d 1357, (Fed Cir

2006), the issue was whether the applicant had adequately described inactivated pox vaccine through disclosure of a herpes vaccine with a deleted essential gene in view of the knowledge of one of ordinary skill.

As illustrated by the above cases, the heightened standard of *Eli Lilly* requiring that inventions directed to DNA or protein sequences be supported by an exact description of its sequence or structure has only come into question where *ipsis verbis* support for a claimed sequence was lacking. Certainly, the written description standard set forth in *Eli Lilly* should be satisfied where the applicant has provided *ipsis verbis* support for a claimed biological sequence. Indeed, describing a DNA or protein molecule in terms of its sequence is the most exacting form of description available.

In the present case under appeal, Examiner has rejected claims 29-30 as allegedly failing to meet the written description requirement of 35 U.S.C. §112. Examiner claims that the "new limitation" of amino acids 11-390 of SEQ ID NO: 4 does not have support in the specification as originally filed. However, amino acids 11-390 of amended SEQ ID NO: 4 are identical in both length and content to amino acids 1-380 of SEQ ID NO: 4 as originally claimed in the priority application, 09/804,690. This parent application is in turn identical in content to antecedent applications 09/146,187, 08/977,918 08/670,274 and 08/585,758 filed January 16, 1996, and claiming the benefit of USSN 60/006,856. Accordingly, a new limitation could not have been added to these claims since the amino acid sequence claimed has remained effectively unchanged. At the very least, since

Appellant originally described the protein sequence corresponds exactly to amino acids 11-390 of SEQ ID NO: 4, Appellant must be entitled to claim sequences comprising the exact sequence for which there is *ipsis verbis* support. Assuming for the sake of argument that Appellant had not amended SEQ ID NO:4 to contain the additional ten amino acids, there could be no basis to reject Appellant's claim to amino acids 1-380 as originally described.

The Examiner further argues that Appellant has allegedly failed to provide adequate written description support for the supposed genus comprising amino acids 11-390 of SEQ ID NO: 4. The Examiner argues that this sequence comprises a genus of sequences since it does not encode the full-length protein (1-390). However, Examiner has failed to establish that there are examples of species other than the full-length protein that would lack the functionality shown. A claim to a protein sequence comprising more than 97% (380/390) of the full-length human protein is unlikely to describe any more "species" than the full-length protein itself.

Even assuming, without accepting, that that the full-length protein (the only example cited by Examiner) is a species embraced by the claim to amino acids 11-390 of SEQ ID NO: 4, Appellant has provided "sufficiently detailed, relevant identified characteristics" for the claimed sequence to properly embrace the full-length protein. In the application as filed, the specification clearly demonstrates an appreciation that the DNA and protein sequences correspond to the human Tsg101 gene, that the DNA and

protein sequences have a high degree of homology to the known mouse sequence, that loss of the Tsg101 gene is associated with a variety of human cancers, and that the human and mouse sequences share conserved functional domains (including a coiled-coil domain containing a leucine zipper and a proline-rich region). See specification, p. 6. Therefore, without question, the protein sequence of claims 29-30 clearly describes the only known member of the supposed genus corresponding to the full-length Tsg101 gene. Not only has Appellant disclosed Tsg101 in structural terms comprising 97% of the protein, Appellant has further provided sufficient identifying characteristics of the protein to unquestionably show that the claimed sequence corresponds to the human Tsg101 gene.

Therefore, from the Appellant's original disclosure, a person of ordinary skill in the art would reasonably conclude that Appellant was in possession of the Tsg101 protein sequence at the time of filing. At the very least, Appellant was clearly in possession of the protein sequence comprising amino acids 11-390 of SEQ ID NO: 4. Accordingly, Examiner's denial of §112 written description support for the disclosed sequence should be reversed.

B. Non-compliance with the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(e) and 120

For the foregoing reasons, Appellant is entitled to claim a protein sequence comprising amino acids 11-390 of SEQ ID NO: 4 since this sequence is supported by the

identical sequence provided by amino acids 1-380 of SEQ ID NO: 4 as originally filed. By extension, therefore, Appellant is entitled to claim priority to the earlier identified applications (U.S. App. No. 09/804,690 filed on 3/12/01; U.S. App. No. 09/146,187 filed on 09/01/98; U.S. App. No. 08/670,274 filed on 01/13/96; 08/585,758 filed on 01/16/96; U.S. Prov. App. No. 60/0006856 filed 11/16/95) since these applications also describe the identical protein sequence corresponding to amino acids 11-390 of SEQ ID NO: 4. Therefore, Examiner's refusal to allow the Appellant to claim the benefit of the earlier filed applications should be reversed.

C. Rejections of Claims 29 and 30 under 35 U.S.C. § 102(b) as anticipated by GenBank referencing Accession No. U8213 and U.S. Patent No. 5,892,016 (Brie et al.)

Claims 29 and 30 stand rejected as met by prior art having an effective date well after the 1996 filing date of Applicants' first full utility disclosure of the exact subject matter claimed. Since Appellant is entitled to claim the benefit of the earlier identified applications having filing dates that antedate the cited references, the GenBank sequence for Deposit Accession No. U8213 (dated 06/04/98) and U.S. Patent No. 5,892,016 (Brie et al. dated 04/06/99) are not available as references since they do not qualify as prior art under 35 U.S.C. §102. Accordingly, Examiner's rejection under 35 U.S.C. §102(b) should be reversed.

D. Rejection of Claim 30 under 35 U.S.C. § 101 as being directed to non-statutory subject matter

The Examiner characterizes claim 30 as lacking a recitation to "sufficiently distinguish the protein as it exists naturally." Respectfully, this is not an accurate characterization of the law. Either the claim embraces the natural product, or it does not. There is no sliding scale of distinction. If the natural product is not embraced, and the examiner does not dispute that TSG101, in its natural state, does not occur "free of other proteins and polypeptides" then the claim is directed to patentable subject matter.

In 1980, the Supreme Court in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), held that non-naturally occurring microorganisms fall within the definition of patentable subject matter under 35 U.S.C. §101. Since that time, the Board of Patent Appeals and Interferences has extended the holding of *Chakrabarty* to include multicellular organisms. See *Ex parte Hibberd*, 227 U.S.P.Q. (BNA) 443 (BPAI 1985); See also *Ex Parte Allen*, 2 U.S.P.Q.2d (BNA) 1425 (BPAI 1987). The Court in *Chakrabarty* made clear that "[i]n choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Chakrabarty*, 447 U.S. at 308. The Court further explained that "Congress intended statutory subject matter to 'include any thing under the sun that is made by man.'" *Id.* at 309. Of course, the scope of patentable subject matter is not unlimited. "The laws of nature, physical phenomena, and abstract

ideas have been held not patentable." *Id.* at 309.

On the other hand, courts have long held that a 'composition of matter,' which might otherwise be considered a prohibited 'product of nature,' will qualify as patentable subject matter under §101 if claimed in a sufficiently purified or isolated form. See *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95 (SDNY 1911); *Merck & Co. v. Olin Mathieson Chemical Co.*, 253 F.2d 156 (4th Circuit 1958); *In re Sune Bergstrom and Jan Sjovall*, 427 F.2d 1394 (CCPA 1970). Indeed, it has become conventional practice to use the terms "isolated" or "purified" to modify claims directed to chemical or biotechnological compositions as a way of meeting the statutory subject matter requirement of §101. See e.g. *Amgen v. Chugai Pharmaceuticals*, 927 F.2d 1200 (Fed. Cir. 1991). However, it has never been held that those exact terms are required to obtain patentability of a claim for a composition of matter that may exist in some form in nature.

The Examiner in this case has rejected claim 30 under §101 for allegedly claiming a naturally occurring product. Claim 30 recites, "A polypeptide comprising the sequence of amino acid residues 11-390 of SEQ ID NO: 4, free of other proteins and polypeptides." Examiner argues that Appellant has not shown that the polypeptide "free of other proteins and polypeptides" does not exist in vivo. However, Examiner has misapplied the appropriate burden. "The examiner bears the initial burden ... of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445, (Fed. Cir. 1992). As stated in MPEP 2106 IV.D., "[i]f the record as a whole suggests that

it is more likely than not that the claimed invention would be considered a practical application of an abstract idea, natural phenomenon, or law of nature, then USPTO personnel should not reject the claim." MPEP 2106 IV.B. further states that "the burden is on the USPTO to set forth a *prima facie* case of unpatentability."

Thus, according to established USPTO procedure, the burden rests initially on the Examiner in this case to show by a preponderance of the evidence that the polypeptide sequence of claim 30 *does* exist in nature free from other proteins. In doing so, the Examiner will have to overcome existing evidence showing the Tsg101 protein is associated with other proteins in the cell. Examiner has not made such a showing and instead places the initial burden on the Appellant. Therefore, until the Examiner has met the initial burden of making out a *prima facie* case, the rejection of claim 30 for non-statutory subject matter under §101 should be withdrawn.

E. Restriction Requirement

In response to the newly added claims, the Examiner has required restriction between:

Group I – the polypeptide of claims 29-30.
Group II – the complex of the antibody/polypeptide of claims 31-32.
Group III – the antibody of claims 33-34.

A restriction requirement is not subject to review on appeal, but rather by petition.

Accordingly, Claims 31- 34 are not properly before the Board, as withdrawn. Nonetheless, Appellant has not cancelled the claims, nor sought review by petition, since it is believed that Claims 29 and 30 are of patentable character, and that upon reversal of the rejections advanced, the Examiner will have opportunity to reconsider his novel approach of specifying that a polypeptide is patentably distinct from the antibody (uncharacterized) raised against that polypeptide.

VIII. SUMMARY

On the basis of the foregoing, Appellant submits that the subject matter claimed is described, and has been described, in the application as filed, in a continuous and properly recited string of parent applications since at least 1996. The function and character of the subject matter claimed, the polypeptide of residues 11 – 390 of SEQ ID No 4 have been described in as much detail as the specific structure. The requirements of 35 USC ' 112, first paragraph are accordingly met, and Applicants are entitled to an effective filing date for these claims of 1996. As such, they are not subject to rejection over the art advanced. And notwithstanding "how" different they are from the naturally occurring Tsg101, they are different – this is sufficient to qualify the claims under 35 USC '101. The outstanding rejections should be reversed, and the case returned for

further examination, including reconsideration of a restriction requirement that holds, quite contrary to established law, that a polypeptide and the antibody raised against are patentably distinct inventions.

Please charge any additional fees due or credit any overage to Deposit Account 10-0233-FUNC-0027-CO5.

Respectfully submitted,

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IX. CLAIMS APPENDIX

1-28. (Cancelled)

29. (Previously Presented) An isolated polypeptide comprising the sequence of amino acid residues 11-390 of SEQ ID NO:4.

30. (Previously Presented) A polypeptide comprising the sequence of amino acid residues 11-390 of SEQ ID NO:4, free of other proteins and polypeptides.

31. (Previously Presented) A complex comprising the polypeptide of claim 29 and an antibody bound thereto.

32. (Previously Presented) The complex of claim 31, wherein said antibody is a monoclonal antibody.

33. (Previously Presented) An antibody which binds to the polypeptide of claim 29, to form the complex of claim 32.

34. (Previously Presented) The antibody of claim 33, wherein said antibody is a monoclonalantibody.

X. EVIDENCE APPENDIX

A. OFFICE ACTIONS AND AMENDMENTS/RESPONSES

1. Amendment of February 26, 2007.

2. Final Office Action of April 19, 2007

3. Specification as originally filed in parent application 09/804,690 and continuation grandparent applications 09/146,187; 08/977,918; 08/670,274 and 08/585,758 filed January 16, 1006. an

B. REFERENCES RELIED UPON BY THE EXAMINER

1. GenBank referencing Accession No. U8213 (dated June 4, 1998).

2. U.S. Patent No. 5,92,016 (**Brie et al.**).

C. REFERENCES CITED BY APPELLANTS

None

D. CASES CITED IN THE BRIEF